CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TRICLOPYR (GARLON)

SB 950-227, Tolerance #417[1]
Chemical Code #: 002131

October 27, 1986
Revised 8/24/87, 9/7/88, 6/5/90, 5/3/96, 4/2/97, 2/10/00

I. DATA GAP STATUS

Combined (chronic/oncogenicity) rat::	No data gap, no adverse effect
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome aberration:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T000210
Revised Toxicology Summary prepared by M. Silva, 6/90; H. Green & M. Silva, 5/3/96, Gee, 4/2/97; M. Silva, 2/10/00.

Rectified through volume 417-156 record # 156807 and volume 51566-042 record # 152162.

Triclopyr, triethylamine salt, CC 2131, Tolerance 417, and the butoxyethyl ester, CC 2170, Tolerance

51566, have been grouped for purposes of toxicological testing. See memorandum of June 13, 1994. **NOTE: Studies are for DPN #417 (triclopyr), unless otherwise indicated.**

II. TOXICOLOGY SUMMARY

COMBINED RAT

Subchronic Study:

51566-026 129424 "Triclopyr Butoxyethyl Ester (Triclopyr BEE): Subchronic Dietary Toxicity Study in Fischer 344 Rats," (Barna-Lloyd, T., Yano, B.L. and Rachunek, B.L., Health and Environmental Sciences - Texas, The Dow Chemical Company, Freeport, TX, March 20, 1992; Study ID#: K120085011). Triclopyr butoxyethyl ester (BEE, 94.4% pure) was fed in diet to Fischer 344 rats (10/sex/dose) at 0, 7, 28, 70 or 350 mg/kg/day for 13 weeks. The FIFRA Guideline recommended parameters were examined. NOEL = 28 mg/kg/day (Body weights and food consumption were decreased at 350 mg/kg/day in both sexes. Kidney weights and degeneration/regeneration of the descending portion of the renal proximal tubules occurred in males at $\geq$ 70 mg/kg/day and in females at 350 mg/kg/day. Increased ALP, ALT and AST (liver damage), increased relative liver weights and histopathologic alterations (hepatocellular hypertrophy with eosinophilia, necrosis) occurred in males ($\geq$ 70 mg/kg/day) and females (350 mg/kg/day).) No adverse effect indicated. These data are supplemental (summary worksheet only). M. Silva, 5/2/96.

Combined Study:

** 046, 054 054226, 064270 "Triclopyr; 2-Year Dietary Chronic Toxicity-Oncogenicity Study in Fischer 344 Rats," (Eisenbrandt, D.L., Firchau, H.M., Wolfe, E.L. and Landry, T.D., Dow Chemical, Lab no. HET K-042085-026, 1-27-87). Triclopyr (> 98% pure, LOT #: AGR 204229) was fed in the diet to Fischer 344 (70/sex/group) at 0 (vehicle = acetone), 3, 12 or 36 mg/kg/day. 10/sex/group were sacrificed at 6 months and 12 months. **No adverse effect.** NOEL = 3 mg/kg/day (An increase in kidney weights was observed in males at two years, along with degeneration of the proximal tubule at the high dose at 6 and 12 months but not at 2 years. Age-related increase pigmentation of the proximal tubules in all doses in females at two years and in high dose females at 6 and 12 months was observed which was not accompanied by histological or functional change.) Originally reviewed as unacceptable but upgradeable (CDFA requested submission of a description of the ophthalmological examination as well as the results. Shimer & Gee 8/87). Upon receipt and evaluation of the requested information (054 064270), this study is now **acceptable**. Kishiyama & Silva, 8/31/88. This study was subsequently re-evaluated and the adverse effect flag has been removed. M. Silva, 5/31/90.

CHRONIC RAT

See combined, rat study **046 054226** (above).

003 986931 "Report to Dow Chemical U.S.A.: Two-Year Chronic Oral Toxicity Study with Dowco 233 (Triclopyr) in Albino Rats." (IBT, 4/19/78) Triclopyr, no purity stated; fed to rats for two years at 0, 3, 10 or 30 mg/kg body weight, 50/sex/group; UNACCEPTABLE due to major variances (no

analysis of diet, no evidence m.t.d. was approached.) Kidney weight increased at high dose but significance without histopathology or clinical chemistry findings questionable. NOEL not established. JR(G), 6-11-85.

EPA 1-liner: Supplementary. Validated by EPL - no effect on hematology, clinical chemistry or urinalysis at 30 mg/kg in diet (HDT).

016 005911 Histopathology for 986931.

026 031048 Histopathology for 986931.

031 035636 See 986931. Includes statistical analyses.

031 035635 See 986931. Histopathology tables for control and high dose groups for 986931.

031 035274 See 986931. Sponsor validation of the IBT study.

003 986930 Summary of 035274.

031 035629 See 986931. Detailed review with discrepancies noted.

003 986920 Summary of 035629.

030 035273 See 986931. An annotated version of the IBT report including individual data not included with 986931.

002 986814 Summary of 986931.

CHRONIC DOG

Subchronic studies:

002 049469, "Subchronic Dietary Study in Beagle Dogs", (Report of Dow Chemical Company, Midland, MI, Quast et al., 7/21/76). Triclorpyr fed to male and female beagle dogs at 5, 10 or 20 mg/kg/day (4/sex/group) for approximately 7 months. This study did not determine a NOEL. A supplemental study in male dogs was performed to assist in the interpretation of decreased phenolsulfonphthalein (PSP) excretion noted during the original study. This study revealed that a competitive inhibition of PSP excretion may occur in dogs ingesting $\geq$ 2.0 mg/kg/day triclopyr as a result of urinary excretion of the administered triclopyr. Decreased PSP clearance rates in dogs do not necessarily reflect renal toxicity. (no worksheet) JSK, 8/22/88. M. Silva, 8/30/88.

002 986935, "Supplemental Subchronic Dietary Feeding Study in Beagle Dogs", (Dow Chemical Company, Midland, MI, Quast et al., 11/10/77). DOWCO 233, purity not stated, fed at 0, 0.1, 0.5 or 2.5 mg/kg/day for 6 months to 4 beagle dogs/sex/group. The only treatment-related effect noted was a slight decrease in phenolsulfonphthalein (PSP) excretion rate in both sexes of dogs ingesting 2.5 mg/kg/day triclopyr relative to control animals. This study served as a pilot for a one-year dog study.

(no worksheets) JSK, 8/22/88. M. Silva, 8/30/88.

003 986926, "Results of 28-day Test in Rhesus Monkeys Treated Daily via Nasogastric Intubation with DOWCO 233", (Dow Chemical Company, Department of Pathology and Toxicology, Indianapolis, IN, Molello et al., 9/8/76). Triclorpyr, purity not given, was administered by nasogastric intubation at 0, 10, 20 or 30 mg/kg/day for 28 days to 8 female rhesus monkeys (2/group). No significant effects were observed at any dose level (no worksheets). JSK, 8/22/88. M. Silva, 8/30/88.

Chronic study:

** 059 069437, "Triclorpyr: A One-Year Dietary Toxicity Study in Beagle Dogs", (Mammalian and Enviromental Toxicology Research Laboratory, Dow Chemical Co., Project Study ID: K-042085-036, 6/7/88). Triclopyr, purity 98.9%, was fed at 0, 0.5, 2.5 or 5.0 mg/kg/day to male and female beagle dogs (4/sex). **No adverse effect.** NOEL = 2.5 (decreased phenolsulfonphthalein excretion, minimal increases in serum nitrogen and creatinine, and microscopic pigment deposits in the proximal tubular epithelial cells of the kidney groups). **Acceptable**. JSK, 8/22/88. M. Silva, 8/30/88.

ONCOGENICITY, MOUSE

** 053 062098, "Triclopyr: 22-Month Oral Chronic Toxicity and Oncogenicity Study in Mice", (The Institute of Enviromental Toxicology, Kodaira, Tokyo, April, 1987). Triclopyr, purity 98.0%, fed at 0, 50, 250 or 1250 ppm to 60 ICR mice (Jcl:ICR)/sex /group for 95 weeks. NOEL = 50 ppm (5.55 mg/kg/day), (decreased body weight gain in both sexes at 1250 ppm; significant increase in water consumption in males at 1250 ppm; decreased specific gravity of urine from 1250 ppm males; thymus was enlarged in males at 250 & 1250 ppm).
No adverse effect. No oncogenic effect observed. **Not acceptable as a combined** (chronic & oncogenicity) **study** (no ophthalmological exam), **but acceptable as an oncogenicity study.** (JSK, 8/16/88; M. Silva, 8/31/88).

003 986932 "Results of Carcinogenic Study in Mice on Dietary Treatment with Dowco 233 (AGR 134832) (Triclopyr) for Two Years." (Dow, 4/11/79). Triclopyr free acid (98.5% from #54223 in 044) fed in the diet to 50/sex/group at 0, 24, 80 or 240 ppm for 2 years; CDF1/COX strain; UNACCEPTABLE (dose selection not justified, no analysis of diet presented, high background of pulmonary tumors with pulmonary tumors as the principal finding, incomplete report.) See 035275 for more complete version but analysis of diet still missing and problem of tumor incidence not clearly resolved. **ADVERSE EFFECT:** Report suggests increased incidence of lung tumors in mice treated with trichlopyr. NOEL not established for oncogenic effect - increased incidence at all dose levels. Gee, 6/11/85.

EPA 1-liner: Supplementary [in initial review, later accepted.] NOEL for pulmonary tumors not established. Results suggest pulmonary tumor carcinogenic effect. (Need to repeat - clarify incidence of spontaneous tumors.) Reevaluation of lung tumors: Dr. Louis Kasza concluded that the oncogenic potential of Garlon can not be substantiated.

032 035275 See 986932. More text, summary incidence of neoplasms, analysis of feed, concurrent control data.

036 043872, 043873 Missing pages 39-67 for 035275 plus the analysis of oncogenicity by Dr. Louis Kasza of EPA. Submission does not change initial review. JGee, 9-26-86.

026 031049 Supplemental to 035275 and 986932.

002 038817 Summary of 035275 and 986932.

003 986936 Supplemental to 986932.

SUMMARY: Although an adverse effect indication was observed in 003 986932, this was discounted in the acceptable study, 053 062098. In 053 062098 the high dose was 5.2 fold higher than the high dose used in 003 986932, however no oncogenic effects were noted. Therefore, it is concluded that triclopyr does not induce oncogenic adverse effects in mice. Silva, 1988.

REPRODUCTION, RAT

**** 093 134788**, "Triclopyr: Two-Generation Dietary Reproductive Study in Sprague-Dawley Rats," (Vedula, U., W.J. Breslin, B.E. Kropscott and K.E. Stebbins, Dow Chemical Co, Toxicology Research, Laboratory Project ID K-042085-048, K-042085-048P1, K-042085-048G0, K-042085-048G2, K-042085-048W1, K-042085-048W2, 1/25/95). Triclopyr (purity = 99.4%; free acid) was fed in diet to Sprague-Dawley rats (30/sex/dose) at 0, 5, 25 or 250 mg/kg for two generations. **Possible adverse reproductive effect:** Reproductive NOEL = 25 mg/kg/day (Litter size and pup weights were decreased in F1 and F2 at 250 mg/kg/day. Fertility indices (P2) were decreased in both sexes at 250 mg/kg/day.) Parental (Systemic) NOEL = 5 mg/kg/day (Body weights and food consumption were decreased in P1 and P2 (both sexes) at 250 mg/kg. Kidney weights (relative) were increased and liver weights were increased in P1 and P2 (both sexes) primarily at 250 mg/kg/day. **Possible adverse systemic effect:** Increase in renal proximal tubule degeneration was increased at $\geq$ 25 mg/kg/day in P1 and P2 (both sexes).) Pup NOEL = 25 mg/kg/day (Pup body weight and survival was decreased from lactation days 1 through 21.) ACCEPTABLE. (Kishiyama & Silva, 5/1/96).

** 417-004 986940 "Three-Generation Reproduction Study in Rats Dowco 233 - Final Report." (Litton Bionetics, 11/4/76) Triclopyr, lot AGR 134832, 98.5% acid, 2.5% ethyl ester; fed in the diet to 11-12 male and 23 females per group at 0, 3, 10 or 30 mg/kg for 3 generation, 1 litter per generation; initially reviewed as unacceptable based on lack of purity, inadequate histopathology, high dose not high enough, lack of diet analyses. With submission of 044, #s 54223 and 54224, the purity has been defined, analysis of the diet presented, individual body weights and food consumption supplied. The study is upgraded to ACCEPTABLE status based on these submissions and the collective histopathology data. In the reproduction study, histopathology was done on 5/sex in the F2 parents. Reproduction NOEL $\geq$ 30 mg/kg/day. JGee, 6/12/85 and 8/87 and FMartz, 3/86.

EPA 1-liner: Minimum. NOEL > 30 mg/kg/day (HDT); systemic NOEL > 30 mg/kg/day.

029 035272 See 986940. Rewritten version of 986940 with individual data, necropsy and histopathology.

039 043878, 043879 Comment by Dow on review of 035272 and 986940 plus OECD Guidelines of reproduction studies.

044 054223 Composition of lot AGR 134832 and diet analysis.

044 054224 Individual body weights and food consumption for 986940.

002 038820 Summary of 035272 and 986940.

TERATOLOGY, RAT

** 003 986939 "Results of a Teratology Study on Dowco 233 (Triclopyr) in the Rat." (Dow, 1979.) Triclopyr, 98.5%, given by oral gavage to 25/group, days 6-15, at 0, 50, 100 or 200 mg/kg/day; fetotoxic NOEL = 100 mg/kg/day; maternal NOEL = 50 (body weight gain); ACCEPTABLE version is 35271; effects on fetuses at 200 mg/kg/day judged to reflect maternal toxicity. JGee, 6-11-85.

EPA 1-liner: Minimum. Terata NOEL $\geq$ 200 mg/kg (HDT); fetotoxic NOEL = 50 mg/kg/day [in view of the LEL, this could be in error]; fetotoxic LEL = 200 mg/kg/day (retarded ossification of skull bones); maternal NOEL < 50 mg/kg/day (decreased body weight gains, food consumption.)

029 035271 See 986939, Complete rewrite of 986939 with data required to make 986939 an acceptable study.

037 043874, 043875 Comments by Dow regarding adverse effects identified by CDFA in reviews of 986939, a journal article on maternal toxicity and fetal malformations and a summary of abnormalities in fetuses from control Sprague-Dawley rats. With this submission, the potential adverse effect identified in the initial review of 986939 is acknowledged as due to the maternal effect and the developmental NOEL is higher than the maternal NOEL.

002 038819 Summary of 035271.

** 088 130203, "Triclopyr Triethylamine Salt: A Study of the Effect on Pregnancy of the Rat", (A.M. Bryson, Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report # DWC 645/646/931358, 9 March 1994). Triclopyr triethylamine salt (triclopyr TEA; 46.5% pure) was administered by gavage to mated Crl:CD*(SD)BR VAF/Plus (25/dose) at 0 (0.5% carboxymethylcellulose), 30, 100, and 300 mg/kg/day on gestation days 6 through 15. **Maternal NOEL =** 30 mg/kg/day (Decreased bodyweight gain at 300 mg/kg/day, with increased water consumption at $\geq$ 100 mg/kg/day was observed. Relative liver and kidney weights were increased at 300 mg/kg/day. One sacrifice in extremis occurred at 300 mg/kg/day). **Developmental NOEL =** 100 mg/kg/day (Decreased mean fetal weights, along with reduced ossification of sacrocaudal vertebral arches and cranial centers, and unossified sternebrae were noted at 300 mg/kg/day). No adverse effect. Acceptable. (Green & Silva, 4/18/96).

51566 - No record #: A letter from DowElanco was submitted which provided preliminary information regarding a triclopyr butoxyethyl ester (TBE) rat teratology study and indications of possible adverse effects. Rats received TBE by gavage at 0, 30, 100 and 300 mg/kg/day during days 6-15 of pregnancy. At 300 mg/kg/day there were 3 deaths, lower mean bodyweights, lower food consumption and decreased water consumption. Liver and kidney weights were increased at 300 mg/kg/day. Post implantation loss was increased at 300 mg/kg/day. Mean litter weight and fetal weight were also decreased at 300 mg/kg/day. At 300 mg/kg/day, proportion of malformations in litters/fetuses was increased (microphthalmia/anophthalmia, retinal folding and cleft palate). Other cranio-facial abnormalities at 300 mg/kg/day were misshapen lower jaw, hydrocephaly, rhinencephaly and agnathia (single litters affected in each case). A single fetus in each of two litters at 100 mg/kg/day had bilateral anophthalmia or retinal folding, cranioschisis and misshapen lower jaw, respectively. There was a higher proportion of fetuses/litters at 300 mg/kg/day with reduced ossification of the sacrocaudal vertebral arches, pelvic girdle, digital centers and unossified sternebrae. In addition, there was an increased incidence of fetuses/litters with one additional thoracolumbar vertebra and extra ribs at this dosage. At 100 mg/kg/day, there was a higher proportion of fetuses/litters with reduced ossification of the sacrocaudal vertebral arches and pelvic girdle with a single instance of an additional thoracolumbar vertebra. The incidence of unossified sternebrae was increased at 100 mg/kg/day. Ossification changes at 30 mg/kg/day were equivocal. The study was expected to be completed as of November, 1994. (No worksheet). M. Silva, 5/1/96.

TERATOLOGY, RABBIT

** 058 069436, "DOWCO 233: Oral Teratology Study in New Zealand White Rabbits", (Mammalian & Enviromental Toxicology Research Laboratory, The Dow Chemical Company, Project study ID: HET-K-042085-042, 4/25/88). DOWCO 233, purity 98.8%, was administered by gavage at 0 (corn oil), 10, 25 or 75 mg/kg/day during days 6 through 18 of gestation to 16 artificially inseminated New Zealand White rabbits/group. **No adverse effect.** Maternal NOEL = 25 mg/kg/day (one rabbit from 75 mg/kg group died at gestation day 18 and found to have dark red urine in the bladder; similar effects were reported in previous rabbit studies with the administration of triclopyr at 100 and 200 mg/kg/day). Developmental NOEL > 75 mg/kg/day (no evidence of embryotoxicity or fetotoxicity). **Acceptable.** (JSK, 8/17/88). M. Silva, 8/31/88.

056 065569, This document contains summaries of two rabbit teratology studies and the protocol for a study entitled "DOWCO 2333: Oral Teratology Study in New Zealand White Rabbits.": An initial teratology study summary, by Smith et al., 1975 (study ID not given) was presented. Triclopyr, suspended in corn oil, was administered at 0, 25, 50 and 100 mg/kg/day to artificially inseminated New Zealand White Rabbits on days 6 through 18 of gestation. A high incidence of mortality in all treatment groups, ranging from 33% at 25 mg/kg/day to 53% at 100 mg/kg/day was observed. No indication of fetotoxicity or teratogenicity was observed in any dose group. (no worksheet) JSK, 8/17/88. M. Silva, 8/31/88.

A subsequent teratology study summary, by Haney et al., 1984 (study ID: not given) was presented. Triclopyr, purity not given, was administered at 0, 10 or 25 mg/kg/day on days 6 through 18 of gestation to 20 mated New Zealand White rabbits. A maternal mortality of 30% was observed in the 25 mg/kg dose level. Maternal weight gain during days 14 through 18 was lower (not statistically significant) in both treatment groups, than the control. No indication of fetotoxicity or teratogenicity

was observed. (no work sheet). JSK, 8/17/88. M. Silva, 8/31/88.
NOTE: The true cause of mortality observed in the two teratology/rabbit studies remains in question. The report states a possible relationship of doe health status and high mortality .

058 069436, Appendix B, Page 176, "DOWCO 233: Oral Teratology Probe Study in New Zealand White Rabbits", (Mammalian & Enviromental Toxicology Research Laboratory, The Dow Chemical Company, study ID: HET-K-042085-041, 4/25/88). DOWCO 233, purity 98.8%, was administered by gavage at 0, 25, 50, 100 or 200 mg/kg/day to 6-7 inseminated New Zealand White rabbits/group on gestation days 6 through 18. Body weight and body weight gain decreased at 200 mg/kg (statistically significant) and 100 mg/kg (not statistically significant). Maternal mortality was observed at 100 and 200 mg/kg/day (50% & 71%*). These animals experienced a decrease in body weight and rapid clinical deterioration before death. Response to DOWCO 233 appeared to be an all-or-none phenomena. No evidence of embryotoxicity, fetotoxicity or teratogenic effects was reported. Due to excessive mortality at 100 and 200 mg/kg/day, 75 mg/kg/day was selected as the high dose level for the main study. (no worksheet) JSK, 11/31/81. M. Silva, 8/31/88.

* Record 056 065569 page 2 states "treatment-related mortality was observed with 6 of 7 rabbits given 200 mg/kg/day. This calculates 85.7% instead of 71% as reported.

003 986938 "Effect of Dowco 233 (Triclopyr) on Pregnancy of the New Zealand White rabbit." (Huntingdon Research Centre, 8/8/79). Triclopyr, lot AGR 134832 (98.5% acid from 044 54223); given by oral gavage to 20 per group, days 6 - 18, at 0, 10 or 25 mg/kg/day; UNACCEPTABLE (dose selection - high dose too low, two doses only, no analysis of dosing solutions, high mortality due to enteric disorder in all groups.) See 35270 for appendices with individual data. Developmental toxicity NOEL $\geq$ 25 mg/kg/day. JGee, 6-11-85 JAParker, 10-23-86.

EPA 1-liner: Minimum. Teratogenic NOEL $\geq$ 25 mg/kg/day (HDT); fetotoxic NOEL $\leq$ 10 mg/kg/day (LDT).

029 035270 See 986738. Appendices with individual data.

003 986937 "The Effect of Dowco 233 Herbicide (3,5,6-Trichloro-2-pyridyloxyacetic Acid) on the Developing Embryo and Fetus of Pregnant Rabbits." (Dow Chemical Co., 2/13/75) Dowco 233, GHC 25-1-47, > 95%, Lot AGR 134832, was administered by oral gavage to groups of 15 New Zealand White pregnant rabbits, 2 ml/kg, at 0 (corn oil), 25, 50 or 100 mg/kg/day on day 6-18 of gestation. Maternal NOEL < 25 mg/kg; Developmental NOEL > 100 mg/kg; high mortality was thought to be due to high volume of corn oil, survival was 14, 11, 3 and 8 for control, low, mid and high dose, respectively. UNACCEPTABLE (insufficient number of litters, no analysis of dosing solutions, complications due to corn oil as vehicle.) JGee, 8/21/87.
EPA 1-liner: Supplementary. Teratogenic effects not observed in survivors at up to 100 mg/kg/day (HDT). No data on teratogenic parameters reported for animals that died. Heavy mortality at all dose levels (25, 50 and 100 mg/k/day) and among controls.

045 054225 Supplemental to 003 986937. Contains individual data.

037 043876 Comments by Dow on the review of the rabbit teratology study, 986937. No change

in the status.

056 065569 "DOWCO 233: Oral Teratology Study in New Zealand White Rabbits," (Dow Chemical Company, 1/5/88). This volume contains the proposed protocol for a rabbit teratology study (058 069436) which has been completed and evaluated by CDFA. M. Silva, 8/31/88.

002 038818 Summary of 986937.

** 51566-027 130201, "Triclopyr Butoxyethyl Ester: A Study of the Effect on Pregnancy of the Rabbit", (A.M. Bryson, Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report # DWC 650/643/931352, 9 March 1994). Triclopyr butoxyethyl ester (triclopyr BEE; 96.98% pure) was administered by gavage to mated New Zealand White rabbits (16-17/dose) at 0 (0.5% carboxymethylcellulose), 10, 30, and 100 mg/kg/day on gestation days 6 through 18. **Maternal NOEL =** 30 mg/kg/day (Increased maternal death, resorptions, post implant loss % and decreased number of litters, with smaller mean live litter size occurred at 100 mg/kg/day.) **Developmental NOEL =** 30 mg/kg/day (There was an increased incidence in skeletal anomalies and variants at 100 mg/kg/day.) **Adverse teratogenic effects are not indicated** below maternally toxic levels. **Acceptable**. (Green & Silva, 4/19/96).

** 088 130202, "Triclopyr Triethylamine Salt: A Study of the Effect on Pregnancy of the Rabbit", (A.M. Bryson, Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report # DWC 642/641/659/931914, 9 March 1994). Triclopyr triethylamine salt (TEA, 46.5% pure) was administered by gavage to mated New Zealand White rabbits (16/dose) at 0 (0.5% carboxymethylcellulose), 10, 30, and 100 mg/kg/day (equivalent to 0, 7, 22 and 72 mg triclopyr acid) on gestation days 6 through 18. **Maternal NOEL =** 30 mg/kg/day (There was 1 maternal death and 1 sacrifice in extremis at 100 mg/kg/day. Increased abortions, decreased body weight gain and food consumption was observed at 100 mg/kg/day. Kidney and liver weights were increased at 100 mg/kg/day.) **Developmental NOEL =** 30 mg/kg/day (Decreased fetal weights were observed at the high dose level). **Adverse fetal effects are not indicated below the maternally toxic dosing level. Acceptable**. (Silva & Green, 4/17/96).

GENE MUTATION

004 986943 "In vitro and subacute in vivo Host-Mediated Assay for Mutagenesis - final report - Compound Dowco 233 (Triclopyr)." (Litton Bionetics, 11/6/73.) Triclopyr, no purity stated; Salmonella strains TA1530 and G46; host-mediated assay in male mice given 0, 0.7, 7.0 or 70.0 mg/kg by oral gavage and injected i.p. with bacteria which were tested after 4 hours for mutagenicity. Saccharomyces D3 also included. Direct assay with 0.1 ml saturated solution. Results expressed as (+) or (-) -- no data. UNACCEPTABLE (use of early strains, no data, test article not described,) Insufficient information for independent evaluation. JGee, 6-12-85.
EPA 1-liner: Minimum. Negative.

** 004 986942 "Ames Metabolic Activation Test to Assess Potential Mutagenic Effect of Dowco 233." (Huntingdon Research Center, 11/5/79). Triclopyr, no purity stated; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without activation at 0, 10, 100, 1000 or 10,000 ug/well in triplicate with a repeat with TA1535; ACCEPTABLE. JGee, 6/12/85.

EPA 1-liner: Supplementary. No mutations induced with and without activation.

004 038822 "Report of Mutagenicity on Triclopyr in Bacterial Test System: Reversion Test with Salmonella." (Dow, 9/4/78). Triclopyr, 98%. Salmonella strains TA98 and TA100, tested at 0, 5, 10, 50, 100 or 500 ug/plate in duplicate with and without activation with no repeat trial and no increased reversion reported. UNACCEPTABLE (no repeat trial, too few plates, no justification for high concentration.) JGee, 6-12-85.
No EPA 1-liner.

033 035276 Duplicate of 986943.

51566-025 129413, "Report of Mutagenicity Test on Triclopyr Butoxyethyl in Bacterial Test System", (Y. Shirasu, M. Moriya, and T. Miyazawa, The Institute of Environmental Toxicology, Japan, 4 September 1978). Triclopyr, butoxyethyl (99% pure) was used in the reversion assay with Salmonella typhimurium strains TA98 and TA100 (duplicate) for 2 days at 0 (DMSO), 10, 50, 100, 500, 1000, and 5000 ug/plate in the presence and absence of activation (rat liver S-9). A spot test was performed with triclopyr butoxyethyl (0.02 ml in DMSO) in a recombinational repair system with mutant (H17) and recombinational repair deficient mutant (M45) of Bacillus subtilis at 0, 1, 5, 10, 25, 50 and 100% triclopyr, butoxyethyl (% v/v). Kanamycin (10 ug/disk) was used for a negative control and mitomycin C (0.1 ug/disk) was a positive control. There was no increase in gene mutation. **Unacceptable** and not upgradeable (strains TA1535 and TA1537 were not included; incomplete description of methods; insufficient numbers of replicates were performed for both tests). (Green & Silva, 4/23/96).

CHROMOSOME ABERRATION

004 986944 "Dominant Lethal Assay for Mutagenesis - Final Report - Compound Dowco 233 (Triclopyr)." (Dow, 11/19/73). Dominant lethal in Sprague-Dawley rats; triclopyr (no purity stated), 10 males/group at 0, 0.7, 7.0 or 70.0 mg/kg by oral gavage for 5 consecutive days; mated 1:2 females for 7 weekly periods; TEM as positive control. Results "indicate a weak/positive dominant lethal action." UNACCEPTABLE (dose selection with inadequate high dose for m.t.d; insufficient number of females per group, no individual mating data.) [See 986945.] JGee, 6/12/85 and FMartz, 3/2/86.
EPA 1-liner: Minimum. Weak positive effect. Trend toward increase in resorptions at 7 and 70 mg/kg.

033 035278 Revision of 986944, dominant lethal. JGee, 9/30/85.

51566-042 152162 Response from DowElanco regarding the evaluation of the above study, 986944, as indicating a possible adverse effect based on the negative mouse dominant lethal and the negative results for the rat and mouse bone marrow studies. No change in the status of 986944 at this time. See rebuttal document, R970402. Gee, 4/2/97.

** 004 986945 "Dowco 233: Dominant Lethal Study - Mice." (Dow, 9/19/80). Triclopyr, 99%; mouse dominant lethal test with 30 males/group given 0, 3, 15 or 70 mg/kg in the feed over 9 weeks then mated 1:4 females for 2 weeks; TEM i.p. as positive control. No adverse effects are reported.

The study was judged to be ACCEPTABLE although it used an alternative protocol to the usual acute gavage one. The difference in result from that in the rat could be 1) species variation or 2) protocol. The study was done as a follow-up to the rat study [986944] but in mice because a heritable translocation test was included but not completed. JGee, 6/13/85 and FMartz, 3/86.
EPA 1-liner: Acceptable. Negative.

** 033 035279 "Evaluation of Triclopyr in the Mouse Bone Marrow Micronucleus Test." (Dow. 1985). Mouse micronucleus test; triclopyr, lot AGR 204229, 98.1%; 10/sex/group given a single dose by oral gavage at 0, 28, 90 or 280 mg/kg; sacrificed 5/sex/group at 24 and 48 hours post treatment; no increase in micronuclei; % PCE decreased slightly as dose increased in males. ACCEPTABLE. JGee, 9/30/85.

004 986950 "Acute and Subacute in vivo Cytogenetic Study in Rats - final Report- Compound Dowco 233 (Triclopyr)." (Litton Bionetics, 9/14/73). Triclopyr (no purity stated); chromosomal aberration in rats given 0, 0.7, 7.0 or 70.0 mg/kg by oral gavage, 15 males per group with sacrifice of 5 from each group at 6, 24 and 48 hours for acute regimen; for subacute regimen given 5 daily treatments, sacrifice time at the end of the treatment; TEM for positive control; scored 50 metaphase cells for each animal for aberrations and 500 cells for mitotic index (MI); UNACCEPTABLE (no evidence that m.t.d. was approached, no justification for using only males). No adverse effect reported. JGee, 6/12/85.
EPA 1-liner: Minimum. Negative.

033 035277 Revised version of 986950, same data. JR(G), 9/30/85.

** 51566-025 129421, "Evaluation of Triclopyr Butoxyethyl Ester (Triclopyr BEE) in the Mouse Bone Marrow Micronucleus Test", (B. Bhaskar Gollapudi and Yvonne E. Samson, Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, Texas, Report # TXT:K-120085-009, 31 December 1990). Triclopyr butoxyethyl ester (triclopyr BEE, 96.1% pure) was administered in a single dose (gavage) to CD-1 mice (15/sex/dose) at 0 (corn oil), 60, 200, and 600 mg/kg. Bone marrow was sampled from 5 per sex per group at 24, 48, and 72 hours. **Increased frequency of micronucleated polychromatic erythrocytes in bone marrow was not indicated**. **Acceptable**. (Green & Silva, 4/25/96).

SUMMARY: A weak dominant lethal effect was noted in rats given triclopyr by oral gavage. These animals experienced a statistically significant increase in resorptions compared to the control at weeks 5 and 7 postreatment. At the same dose, the effect was not observed in the mouse, however, the route of administration was different (diet) as was the treatment period (5 days for rat versus 9 weeks for mouse). It may be a species difference in sensitivity to Triclopyr. Two other in vivo tests were also negative, one in the mouse and one in rats. Endpoints are different in 035279 & 986950 than in 986944 & 986945, and therefore the tests cannot be directly compared. Considering the insensitivity of the dominant lethal test (in general) and the fact that a positive effect was observed in rat, Triclopyr may induce an possible adverse effect for chromosome mutations. The weight-of-evidence, however, should be considered in the risk assessment process. Silva, 1988; revised by Gee, 4/2/97.

MUTAGENICITY, DNA/OTHER

004 986941 "Report of Mutagenicity Test on Triclopyr in Bacterial Test System: Rec-Assay with B. subtilis." (Dow, 9/4/78) Triclopyr, 98% was tested with B. subtilis strains H17 and M45 at 0, 20, 100, 200, 500, 1000 or 1000 ug/disk, single plates. Kanamycin and mitomycin C were positive controls. No effect was reported but insufficient information for evaluation. UNACCEPTABLE (no repeat trial, single plate per concentration, no activation.) JGee, 6/12/85.

** 040 045392 "Evaluation of Triclopyr in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (Dow, 3/4/86) Triclopyr, 99.0%, in primary rat hepatocytes tested for unscheduled DNA synthesis at 6 concentrations ranging from 5×10^{-6} to 5×10^{-3} M; ACCEPTABLE with no evidence of UDS induction. JGee, 9/26/86.

038 043877 Partial duplicate of 045392.

** 51566-025 129420, "Evaluation of Triclopyr Butoxyethyl Ester (Triclopyr BEE) in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay", (B. Bhaskar Gollapudi, Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX. 77541, Report # TXT:K-120085-008, 28 December 1990). Triclopyr butoxyethyl ester (96.1% pure) was added to rat liver hepatocyte cultures (Sprague-Dawley, outbred Crl:CD BR) for 18 hours in quadruplicate at 0 (DMSO), 1.0, 3.33, 10.0, 33.3, 100.0, 333.0, or 1000.0 ug/ml. 50 cells per slide were evaluated. **Induction of unscheduled DNA synthesis was not indicated**. **Acceptable**. (Green & Silva, 4/24/96).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL INFORMATION

156 156807 “Review of Tumor Data From the Chronic Toxicity/Carcinogenicity Studies of Tryclopyr in F344 Rats and ICR(Jcl:ICR) Mice,” (Goodman, D.G. & Hildebrandt, P.K.; PATHCO, Inc., Ijamsville, MD; PATHCO #: 96-86; 12/10/96). This document contained a re-evaluation by a Cancer Peer Review Committee (CPRC) of tumor data from the rat combined (DPR volume/record #: 417-046, 054/054226, 064270) and mouse oncogenicity (417-053/062098) studies (both are accepted by DPR with no adverse effects). The neoplasms examined included: mammary tumors (rats & mice), adrenal medullary pheochromocytomas, skin papillomas and subcutaneous fibromas (male rats). The weight-of-evidence indicated that the slight increase in mammary tumors was not related to triclopyr treatment in rats and mice; nor were the other tumors observed in rats and mice related to triclopyr treatment. The conclusion was “After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the...CPRC concluded that the increases in tumor incidence were marginal. Based on this marginal response and the absence of any additional suggestion of potential carcinogenicity from structural analogs or genotoxicity, the consensus of the CPRC was to classify triclopyr as a Group D chemical...” These data are supplemental. M. Silva, 2/10/00.